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10/591,993	09/07/2006	Satoshi Kanazawa	80186(302730)	6413

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EXAMINER	
LONG, SCOTT	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,993	KANAZAWA ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, without traverse, of Group I (claims 1-10) directed to a transgenic non-human mammal, in the reply filed on 16 September 2008.

Claim Status

Claims 1-17 are pending. However, claims 11-17 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 3-5, 7-10, 14 and 16 are amended. Claims 1-10 are under current examination.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 7 September 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 7 September 2006 consisting of 1 sheet are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from PCT/JP2005/04007 (filed 8 March 2005). This application also claims benefit from foreign application, JAPAN 2004-066218 (filed 9 March, 2004). The instant application has been granted the benefit date, 9 March 2004, from the foreign application, JAPAN 2004-066218.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The embedded hyperlink is found on page 7, line 32.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 contains parentheses in lines 4 and 5. The examiner considers this to be a typographical error, since the phrase, "having a master switch function..." does not require parentheses to make logical/grammatical sense. Normally, the examiner does not consider phrases in parenthetical phrases to have patentable weight. However, the examiner is interpreting the currently written claim as though no parentheses were present. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claim 3, the phrase "or the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claims 4-8 recites the limitation "the pathological condition" in the 2nd line of each claim. There is insufficient antecedent basis for this limitation in the claim; claim 1 (from which claims 4-8 depend) does not contain reference to "a pathological condition."

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

SCOPE OF ENABLEMENT

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse model for human arthritis whose a genome comprises a foreign DNA consisting of MHC class II transactivator gene, under the control of a type II collagen promoter wherein said mouse, does not reasonably provide enablement for the broad genus of transgenic animals having genetic mutations as described in claim 1.

Furthermore, the specification does not seem to reasonably provide enablement for transgenic non-human mammal comprising (1) an active region of the MHC class II transactivator gene, under the control of a type II collagen promoter, or (2) a mutant MCH class II transactivator gene, under the control of a type II collagen promoter. Additionally, the specification does not seem to reasonably provide enablement for transgenic non-human mammal having the breadth of phenotypes listed in claims 5-8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some

'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

NATURE OF THE INVENTION

The breadth of the claims encompasses a genus of transgenic animals, having foreign DNA selected from the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene , under the control of a type II collagen promoter.

WORKING EXAMPLES & GUIDANCE PROVIDED

The specification clearly describes the phenotype of a transgenic mouse having a heterologous DNA comprising MHC class II transactivator gene (CIITA) under the

control of a type II collagen promoter as exhibiting certain pathological symptoms similar to human rheumatoid arthritis when administered type II collagen (Examples 1-2).

However, the specification does not provide guidance for or a working example for transgenic animals beyond a transgenic mouse having a heterologous DNA comprising MHC class II transactivator gene (CIITA) under the control of a type II collagen promoter. The specification has reduced to practice a single embodiment of the claimed invention, namely a transgenic mouse having a heterologous DNA comprising MHC class II transactivator gene (CIITA) under the control of a type II collagen promoter. Therefore, a skilled artisan would not know how to make embodiments of transgenic animals other than a transgenic mouse.

In addition to the lack of examples of embodiments other than transgenic mice, the specification is limited to a specific example of transgenic mouse. The breadth of the instant claims encompasses transgenic mice, having foreign DNA selected from the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene, under the control of a type II collagen promoter. The specification has not reduced to practice a transgenic non-human mammal comprising (1) an active region of the MHC class II transactivator gene, under the control of a type II collagen promoter, or (2) a mutant MCH class II transactivator gene, under the control of a type II collagen promoter.

The specification contains limited support for transgenic mammals comprising "active regions" and "mutations" of the MCH class II transactivator.

The specification teaches that "[a]ny mutants [of the CIITA gene] can be used as long as they have a function specific to the CIITA gene, that is, a function as a master switch for controlling the expression of the CIITA gene group" (page 8, lines 3-4). The specification does not teach which portions of the CIITA function as a master switch for controlling the expression of the CIITA gene group. Furthermore, the specification does not indicate which functions are encompassed by "a function as a master switch." Since the specification does not teach which portions of the CIITA function as a master switch for controlling the expression of the CIITA gene group, the examiner concludes that a skilled artisan would not know not to make this mouse.

Additionally, the specification has not provided support for the structural regions of the MHC class II transactivator gene which can be considered "active regions." Furthermore, the specification has not specifically defined "active region of the MCH class II transactivator." The specification has not disclosed any specific "active region of" or "mutant" MCH class II transactivator gene which can induce arthritis-like symptoms in a transgenic animal. Additionally, neither the specification nor the art indicate a relationship between the structure of the claimed genus of "active regions" or "mutants" and the recited induction of rheumatoid arthritis-like symptoms. In particular, there is no indication in the art or specification as to the effect of varying the nucleic acids of the genus of isolated nucleic acids encompassed by the instant claims upon a phenotype having rheumatoid arthritis-like symptoms. Therefore, a skilled artisan would not know how to make this embodiment of transgenic mouse comprising an

active region of the MHC class II transactivator gene under the control of a type II collagen promoter.

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

Because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappel et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al. (J. Clin. Invest.1996; 98, page 1559) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another."

Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1998) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann (1998) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises foreign DNA selected from the group consisting of MHC class II transactivator gene, an active

region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene, under the control of a type II collagen promoter, other than the exemplified transgenic mouse comprising a foreign DNA comprising a MHC class II transactivator gene, under the control of a type II collagen promoter, it would have required undue experimentation to predict the results achieved in any one host animal whose genome comprises foreign DNA selected from the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene, under the control of a type II collagen promoter, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. Therefore, the examiner concludes that a skilled artisan would determine the specific transgenic mouse embodiment of the claimed invention would not be reasonably predictive of all other non-human transgenic animal embodiments.

Moreover, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, J. Mol. Med., 1997, p. 214, *Summary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore,

the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (Journal of Clinical Investigation, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

This is further supported by Pera *et al.* [Journal of Cell Science 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and

laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last paragraph].

In addition to the problems associated with generating various embodiments of non-human transgenic mammals, the instant claims are directed to various phenotypes which are unpredictable or not correlated with animal models of rheumatoid arthritis. The examiner finds the specification supports a particular embodiment of instant claim 1, a transgenic mouse having a foreign DNA, the foreign DNA having MHC class II transactivator gene (CIITA) under the control of a type II collagen promoter. However, even more importantly, this transgenic mouse is shown to be useful as an animal model of human rheumatoid arthritis (Examples). Claim 5 is directed to the transgenic non-human mammal according to claim 1, wherein the pathological condition of human rheumatoid arthritis is a pathologic condition showing one or more of the following:...(1) joint swelling is observed in three places or more in the whole body...symmetry joint swelling is observed. While the instant specification indicates that joint swelling in 3 or more places is characteristic of human rheumatoid arthritis, the instant application does not demonstrate that this characteristic is present in the claimed mammals. Figures 3-4 indicate that measurement of the transgenic mouse's joints were performed, but, since a determination of the development of RA in the mice could be obtained without having joint swelling in 3 or more joints, the examiner concludes that this limitation is not enabled in the claimed mammals. Lindqvist et al. teach that in some mouse models of rheumatoid arthritis, especially collagen-induced arthritis (CIA), symmetric arthritis is not present (page S9, Table 2). The specification's examples do not demonstrate this

symmetric arthritis. Therefore, the examiner concludes that there is some unpredictability in the rheumatoid arthritis mouse model provided in the specification.

In addition, Lindqvist et al. (Trends in Genetics. 2002; S7-S13) indicate that the American College of Rheumatology criteria of classification for rheumatoid arthritis is different from the characterization of CIA (page S9, Table 2), thereby demonstrating some unpredictability in the art of rheumatoid arthritis mouse models. Lindqvist et al. also indicate that there are a few different mechanisms for the induction of arthritis in mice (page S11). Lindqvist et al. also note that mouse models do not perfectly match rheumatoid arthritis (page S11, col.2, Chronicity in Arthritis, parag.1) and that it is important to understand the differences between the various mouse models (page S12, col.1, Perspectives). In fact, Lindqvist et al. teach "transgenic models for arthritis represent a situation of monogenic causes of disease. This is not entirely true, however, as the disease expression in most cases is dependent on the genetic background...[other genes] can also contribute to the obtained phenotypic results. This illustrates the complexity of the genetic susceptibility to arthritis and also the need to cautiousness when interpreting results from genetically manipulated models." (page S12, col.1, Perspectives). Lindqvist et al. seems to be saying that there is highly level of uncertainty in correlating the phenotypes of transgenic mouse models of RA with the disease itself.

Furthermore, since the scope of the claims encompasses non-murine models of rheumatoid arthritis, and the behavior of this transgene in other mammalian models of RA is unpredictable, the examiner believes the instant invention is limited to the

transgenic mouse comprising a MHC class II transactivator gene under the control of a type II collagen promoter having certain phenotypes associated with rheumatoid arthritis. However, the examiner is not sure that all the claimed phenotypes of RA described by claims 4-8 are enabled. Particularly, claims 6 and 8 list angiitis, anemia, and pneumonia as indicative of rheumatoid arthritis. These are not sole indicators of RA, as suggested by the instant claims; they may accompany RA, but can also accompany a variety of other diseases. Therefore, the examiner finds there to be unpredictability regarding enablement of claims 6 and 8, particularly.

CONCLUSION

In conclusion, given the breadth of the claims and the limited scope of the specification, an undue quantity of experimentation is require to make the invention beyond the scope of a transgenic mouse having a heterologous DNA comprising MHC class II transactivator gene (CIITA) under the control of a type II collagen promoter as exhibiting pathological symptoms similar to human rheumatoid arthritis when administered type II collagen. Transgenic mammals other than mice are not enabled. The specification is also not enabled for transgenic mice having (1) an active region of the MHC class II transactivator gene, under the control of a type II collagen promoter or (2) a mutant MCH class II transactivator gene, under the control of a type II collagen promoter. Furthermore, the examiner concludes that some limitations of claims 5-8 are not fully enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fabre et al. (WO98/15626) in view of Osaki et al. (Biochemical Journal. 11 September 2002; 1-34).

Claim 1 is directed to a transgenic non-human mammal comprising a foreign DNA, the foreign DNA having a DNA which is selected form the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene (having a master switch function for controlling an expression of the MHC class II genes), and which is under the control of a type II collagen promoter. Fabre et al. teach production of transgenic donor animals for xenografts comprising nucleic acids encoding a fragment of MHC class II transactivator (CIITA) protein (abstract). In particular, Fabre et al. teach "a transgenic pig, at least some of the cells of which comprising a stably incorporated, functional DNA sequence that encodes a polypeptide that comprises the amino acid sequence of a class II trans activator (CIITA) protein" (page 13, lines 12-15). As the specification does not clearly define " an active region of the MHC class II transactivator gene," the examiner is interpreting the teachings of Fabre et al. directed to a "functional DNA sequence that encodes a polypeptide that comprises the amino acid sequence of a class II trans activator (CIITA) protein," as satisfying this specific claim limitation. Fabre et al. also teach "it is therefore advantageous to incorporate the nucleic acid sequence under the control of a tissue-specific promoter in order to down-regulate MHC II class antigen production in a specific tissue only...there may be used a promoter specific for the organ to be transplanted" (page 14, lines 16-27).

Fabre et al. teach or suggest a transgenic non-human mammal (pig) comprising a foreign DNA, the foreign DNA having a DNA which is an active region of the MHC class II transactivator gene. Fabre et al. further suggests that such transgenic

mammals could have expression of active regions of CIITA under the control of a tissue-specific promoter. Fabre et al. do not explicitly teach that the tissue-specific promoter is the type II collagen promoter.

However, Osaki et al. teach "core promoter of the type II collagen gene" (title) and "Type II collagen is the major collagen synthesized by chondrocytes in mature articular cartilage...[having] stage-specific and tissue-specific expression during chondrogenesis" (page 3, lines 2-8). Osaki et al. are suggesting that collagen type II promoter is specifically active during the formation and maintenance of collagen. Collagen is . Furthermore, Osaki et al. suggest using a type II collagen enhancer (page 3, line 8) as recited in claim 2.

Accordingly, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a transgenic non-human mammal comprising a foreign DNA, the foreign DNA having a DNA which is an active region of the MHC class II transactivator gene, and which is under the control of a type II collagen promoter.

The person of ordinary skill in the art would have been motivated to make those modifications because Fabre et al. teach that such animals are useful for xenotransplantation. While Fabre et al. do suggest tissue-specific expression of active regions of CIITA in transgenic mammals, they do not explicitly teach using type II collagen promoter. However, it would be obvious to use the type II collagen promoter in such transgenic animals when they are used for xenotransplantation of cartilage.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Fabre et al. and Osaki et al. because making transgenic mice having tissue-specific expression patterns was known in the art at the time of the instant invention.

Therefore the transgenic mammal as taught by Fabre et al. in view of Osaki et al. would have been *prima facie* obvious over the transgenic mammal of the instant application.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harton et al. (Molecular and Cellular Biology, Sept. 2000; 20(17):6185-6194) in view of Lindqvist et al. (Trends in Genetics. 2002; S7-S13) and further in view of Otten et al. (Journal of Immunology. 2003; 170: 1150-1157).

Claim 1 is directed to a transgenic non-human mammal comprising a foreign DNA, the foreign DNA having a DNA which is selected form the group consisting of MHC class II transactivator gene, an active region of the MHC class II transactivator gene, and a mutant MCH class II transactivator gene (having a master switch function for controlling an expression of the MHC class II genes), and which is under the control of a type II collagen promoter.

Harton et al. teach class II MHC is involved in rheumatoid arthritis (page 6185, col.1, Introduction, lines 9-11) and CIITA expression is required for expression of class II MHC (page 6185, col.2, Introduction, lines 10-12). Harton et al. demonstrate the nexus between class II transactivator (CIITA) expression for the expression of class II

MHC and it's role with MHC in rheumatoid arthritis. Further, Harton suggests that enhancement of class II MHC through CIITA is involved in critical events of pathogenesis and autoimmune diseases such as RA (page 6191, col.1, last parag.).

Harton et al. does not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter.

Lindqvist et al. teach a variety of mouse models of rheumatoid arthritis. In particular, Lindqvist et al. teach collagen induced arthritis (CIA), in which mice display symptoms similar to human rheumatoid arthritis when injected with type II collagen. Lindqvist et al. also teach in transgenic models of RA, the effect of a specific gene is evaluated for its involvement in the arthritis development (page S8, col.2). Lindqvist et al. teaches "RA is genetically associated with the major histocompatibility complex (MHC) class II" (page S8, col.1, parag.1). Lindqvist et al. teach a transgenic mouse having cartilage-restricted expression (page S9, col.2 and Fig.1).

Lindqvist et al. does not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter, but does suggest other transgenic animal models for RA, including some which have collagen-specific expression. Lindqvist et al. further teaches induction of RA symptoms in the CIA model. Lindqvist et al. also suggests making generic mouse models of RA by expression of "a specific gene." Finally, Lindqvist et al. teach the connection between MHC II expression and rheumatoid arthritis. Additionally, Lindqvist et al. teaches symptoms in mouse models of RA which correspond to claims 5-8 (Table 1).

Otten et al. teach "Increased CIITA and MHC-II expression…occur in autoimmune conditions such as rheumatoid arthritis" (page 1150, col.2, last parag.). Otten et al. also teach a transgenic mouse expressing CIITA in all organs (page 1153, col.1, parag.1). Otten et al. teach "[i]n our transgenic mouse, the CIITA transgene induces MHC-II expression in most cell types" (page 1156, col.2, CIITA transgenic mice section).

While Otten et al. emphasize the affect of CIITA overexpression on immune cell function, it is clear that their transgenic CIITA mouse is suggested as being a model of rheumatoid arthritis. However, Otten et al. do not teach a transgenic non-human mammal comprising CIITA operably linked to collage II promoter.

However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a transgenic non-human mammal comprising a foreign DNA, the foreign DNA having a DNA which is a MHC class II transactivator (CIITA) gene, and which is under the control of a type II collagen promoter.

The person of ordinary skill in the art would have been motivated to make a transgenic mouse comprising a MHC class II transactivator (CIITA) gene which is under the control of a type II collagen promoter. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (transgenic mice comprising CIITA;

nexus between CIITA expression and RA; animal models of RA which include administration of collagen II; and suggestions for joint-specific (collagen) expression of genes in animal models of RA) are taught by Harton or Lindqvist or Otten and further they are taught in various combinations and are shown to be used in mouse models of rheumatoid arthritis. It would be therefore predictably obvious to use a combination of these elements in a mouse models of rheumatoid arthritis.

Some of the symptoms of claims 5-8 not explicitly taught by the animal models described by Lindqvist et al. are a result, not of rheumatoid arthritis, but of secondary factors that can occur in individuals with RA, namely pneumonia and anemia. Therefore, these (claims 6 and 8) would be obvious. Lindqvist et al. teach administration of type II collagen to induce RA in mice models; therefore, the exact dosages (claims 3-4) would be obvious to one of skill in the art.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Harton et al. and Lindqvist et al. and Otten because making transgenic mice having tissue-specific expression patterns was known in the art at the time of the instant invention.

Therefore the transgenic non-human mouse as taught by Harton et al. in view of Lindqvist et al. and further in view of Otten et al. would have been *prima facie* obvious over the transgenic mouse having a phenotype of rheumatoid arthritis-like symptoms of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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